



SYNTHESIS OF NOVEL OXAZOLES AND THEIR HYDRAZONES

Vijay V Dabholkar¹ and Sagir Ahmed Sabir Ali Syed^{1*}

¹Organic Research Laboratory, Department of Chemistry, KC College, Churchgate, Mumbai-20
Mumbai University, Maharashtra, Mumbai (India)

*E-mail: sagir_ab@indiatimes.com

ABSTRACT

2, 4-disubstituted Oxazoles (2) were prepared from Hippuric acid/acetyl glycine, substituted aromatic aldehydes, acetic anhydride and sodium acetate as a catalyst. Further reacting with hydrazine hydrate yielded corresponding hydrazones (3), which on condensation reaction with different aldehydes revealed final Schiff base. The structures of the compounds have been elucidated on the basis of spectral analysis.

Keywords: Hippuric acid, Acetyl glycine, Oxazoles, Hydrazones.

© 2010 RASAYAN. All rights reserved

INTRODUCTION

Substituted Oxazole derivatives are found to be associated with various biological activities such as antibacterial¹, antifungal², antitubercular³, anti-inflammatory⁴. Oxazoles are well known as important structural units in a wide variety of biologically active natural products as well as useful synthetic intermediates⁵⁻⁷. The oxazolone ring occurs naturally and the total synthesis of natural products with a wide variety of biological activities containing Oxazole moiety is an area of intense research. Other applications of Oxazole derivatives include the use as pesticides, fluorescent whitening agents, lubricants, dyes and pigments⁸⁻¹⁶. Therefore, there is considerable interest of having available efficient routes to these heterocycles and better understand their reactivity.

The ability of α , β -unsaturated ketones to react with various nucleophilic reagents prompted us to synthesis some new fused oxazole compounds. Schiff base of 2-methyl / phenyl -4-benzylidene -5-hydrazino -1, 3-Oxazole (4) were obtained by condensing 2-methyl / phenyl-4-benzylidene-5-Oxo-1, 3-Oxazole (2) with hydrazine hydrate and aromatic aldehydes (Scheme-1).

EXPERIMENTAL

Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The purity of the compounds was monitored by thin layer chromatography on silica gel coated aluminium plates (Merck) as adsorbent and UV light as visualizing agent. IR spectra (KBr in cm^{-1}) were recorded on a Perkin-Elmer spectrophotometer in the range of 4000-400 cm^{-1} . ¹H NMR spectra were recorded on a Varian 500 MHz NMR spectrometer using $\text{CDCl}_3/\text{DMSO}-d_6$ as solvent and TMS as an internal standard (chemical shifts in δ ppm).

Synthesis of 2, 4-disubstituted-oxazoles (2)

A mixture of aromatic aldehydes (0.25 moles), Hippuric acid (44.8 gm, 0.25 mole) / acetyl glycine (29 gm, 0.25 moles), anhydrous sodium acetate (15 gm), and acetic anhydride (59 ml) was heated at 110°C, with constant stirring. The mixture become almost solid, and then as the temperature rises, it gradually liquefies and turns deep yellow in color. After completion of the reaction monitored by TLC the reaction is allowed to cool and ethanol (100 ml) is added slowly to the contents of the flask. After allowing the reaction mixture is left to stand overnight, the yellow color product is filtered and washed with ice cold ethanol and finally with boiling water and recrystallized in ethanol to yield 2a.

2-methyl / phenyl-4-Benzylidene-5-hydrazino-1, 3- Oxazole (3)

Mixture of **2** (0.05 mole), Hydrazine hydrate (0.05 mole), Methanol (10 mL) was taken in 100 mL round bottom flask and the mixture was reflux for 1 hr. After monitoring the reaction on TLC, the reaction mixture was cooled and dumped on to ice, filtered and recrystallized from ethanol to yield **3**.

Schiff base of 2-methyl / phenyl-4-Benzylidene-5-hydrazino-1, 3-Oxazole (**4**)

Mixture of **3** (0.05 mole), aromatic aldehydes (0.05 mole), Potassium hydroxide (0.1 mole), Ethanol (10 mL) was taken in 100 mL round bottom flask and the mixture was reflux for 4 hrs. After monitoring the reaction on TLC, the reaction mixture cooled and dumped on to ice, filtered and recrystallized from ethanol to yield **4**.

The physical and characterization data of the compounds **4a-u** are listed in the **Tables I**

Antimicrobial evaluation

Representative samples were screened for their antimicrobial and antifungal activity against gram-negative bacteria, *E. coli* and *P. aeruginosa* and gram-positive bacteria, *S. aureus*, and *C. diphtheriae* using disc diffusion method^{17, 18}. The zone of inhibition was measured in mm and the activity was compared with standard drug. The results of antibacterial screening studies are reported in **Table II**.

RESULTS AND DISCUSSION

The Schiff base of 2-methyl / phenyl -4-benzylidene -5-hydrazino -1, 3-Oxazole (**4**) were obtained by condensation of 2-methyl / phenyl-4-benzylidene-5-Oxo-1, 3-Oxazole (**2**) with hydrazine hydrate followed by different aromatic aldehydes with good yield.

Further, the representative compounds were screened for their antimicrobial activity against gram negative as well as gram positive bacteria, which shows convincing activity.

ACKNOWLEDGEMENT

The authors are grateful to the Principal Ms. Manju J. Nichani and Management of K.C. College, Mumbai for providing necessary facilities. Authors are also thankful to the Director, Institute of Science, Mumbai for providing spectral analyses.

REFERENCES

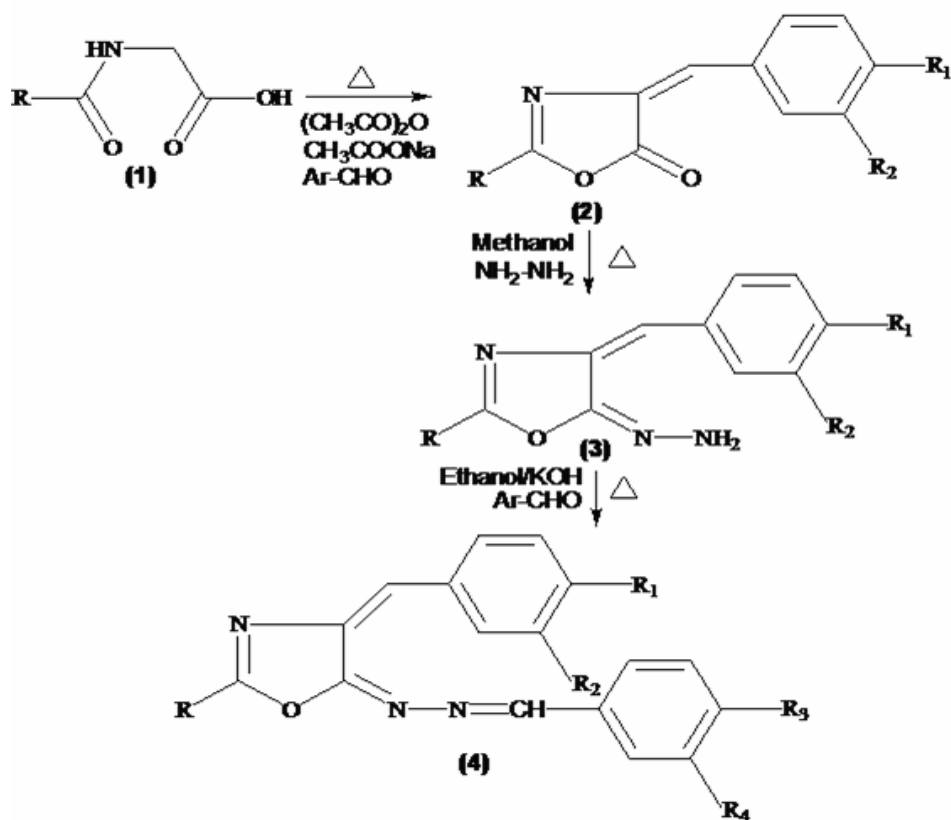
1. K. Tsuji, H. Isgikawa, *Bio-org. Med. Chem. Lett*, **4**, 1601(1994).
2. C. George, N. Martin, R. Ray, *J. Med. Chem.* **16**, 1402(1973).
3. C.G. Anna, I.M.B. Helenam, G.F. Scitt, E.B. Clifton, R.C. Brent, *Tetrahedron Lett*, **46**, 7355(2005)
4. George, C.; Michael, J.F. *J. Med. Chem.* **14** (1971), 1075-77.
5. P. Wipf, *Chem. Rev.*, 2115(1995).
6. S. Cicchi, F.M. Cordero, D. Giomi, *Prog. Heterocycl. Chem*, **12**, 217(2001).
7. J.R. Lewis, *Natural Product Reports*, **12**, 135 (1995); K.J. Doyle, C.J. Moody, *Tetrahedron* **50**, 3761 (1994); G. Videnov, D. Kasier, G. Jung, *Angew. Chem. Int. Ed. Engl.*, **35(13/14)**, 1503(1996); A.R. Katritzky, C. W. Rees, Eds.; *Pergamon Press*: Oxford, Chapter 18(1984).
8. S.A. Lang Jr., Y.I. Lin, in: A.R. Katritzky, C.W. Rees, K.T. Potts (Eds), *Comprehensive Heterocyclic Chemistry*, **Vol. 6**, Pergamon, Oxford, (1984), Chapter 4.16 and Chapter 4.18;
9. T.M.V.D. Pinho E Melo, *Curr. Org. Chem.* **9**, 925 (2005)
10. V.S.C. Yeh, *Tetrahedron* **60**, 11995(2004)
11. Y. Hamada, T. Shioiri, *Chem. Rev.* **105**, 4441(2005)
12. P. Wipf, *Chem. Rev.* **95**, 2115(1995).
13. Vijay V. Dabholkar and Sagar D. Parab, *Indian Journal of Chemistry*, **46B**, 344(2007).
14. Vijay V. Dabholkar and Sushil Kumar J. Mishra, *Indian Journal of Chemistry*, **45B**, 2112(2006).
15. Vijay V. Dabholkar and Sushil Kumar J. Mishra, *Heterocyclic Communication*, **12(3-4)**, 241(2006).
16. Vijay V. Dabholkar and Ashish S. Sanghvi, *Indian Journal of Heterocyclic Chemistry*, **16**, 105(2006).
17. R. Cruickshank, J.P. Duguid and B.P. Marmion, *Medicinal Microbiology*, 12th Edn, **11**, 1975, (Churchill Livingstone, London).
18. B.A. Arthington-Skaggs, M. Motley and C.J. Morrison, *J. Clin. Microbiology*, **38**, 2254(2000).

[RJC-687/2010]

Table-1: Characterization of synthesized Compounds 4

Compd	R	R ₁	R ₂	R ₃	R ₄	m.p (°C)	Spectral data IR (KBr cm ⁻¹)/ ¹ H NMR/ ¹³ C NMR (ppm) in DMSO- <i>d</i> ₆ /C H and N Analysis.
4a	CH ₃	H	H	H	H	220-222	IR: 3031 (CH-Str), 1664 (C=N), ¹ H NMR: 2.1 (s, 3H, CH ₃), 6.9- 7.7(m, 12H, ArH & CH) [Found : C, 74.72, H, 5.23, N, 14.52, C ₁₈ H ₁₅ N ₃ O requires C, 74.70, H, 5.33, N, 14.42 %]
4b	CH ₃	H	H	OCH ₃	H	225-227	IR: 3028 (CH-Str), 1658 (C=N)
4c	CH ₃	H	H	OH	H	240-243	IR: 3125 (OH), 3018 (CH-Str), 1664 (C=N)
4d	CH ₃	OCH ₃	H	OCH ₃	H	238-240	IR: 3031 (CH-Str), 1662 (C=N)
4e	CH ₃	OCH ₃	H	OH	H	228-230	IR: 3138 (OH), 3028 (CH-Str), 1655 (C=N)
4f	CH ₃	OCH ₃	H	OCH ₃	OH	230-232	IR: 3122 (OH), 3018 (CH-Str), 1664 (C=N)
4g	CH ₃	OH	H	OCH ₃	H	225-227	IR: 3132 (OH), 3022 (CH-Str), 1652 (C=N)
4h	CH ₃	OH	H	OH	H	218-220	IR: 3128 (OH), 3025 (CH-Str), 1612 (C=N)
4i	CH ₃	OCH ₃	OH	OCH ₃	H	255-257	IR: 3127 (OH), 3018 (C=CHR), 1664 (C=N), ¹ H NMR: 1.9 (s, 3H, CH ₃), 3.7 (s, 3H, OCH ₃), 3.8 (s, 3H, OCH ₃), 6.8-7.8(m, 9H, ArH & 2CH), 8.2 (br,1H,OH), [Found : C, 65.74, H, 5.24, N, 11.50, C ₂₀ H ₁₉ N ₄ O ₃ requires C, 65.65, H, 5.15, N, 11.42 %]
4j	CH ₃	OCH ₃	OH	OH	H	230-233	IR: 3120 (OH), 3017 (CH-Str), 1660 (C=N)
4k	CH ₃	OCH ₃	OH	OCH ₃	OH	218-220	IR: 3131 (OH), 3018 (CH-Str), 1664 (C=N)
4l	C ₆ H ₅	H	H	OH	H	255-257	IR: 3118 (OH), 3025 (CH-Str), 1652 (C=N)
4m	C ₆ H ₅	H	H	OCH ₃	OH	248-250	IR: 3142 (OH), 3030 (CH-Str), 1660 (C=N)

4n	C ₆ H ₅	Cl	H	H	H	250-252	IR: 3032 (CH-Str), 1647 (C=N), ¹ H NMR: 7.3- 7.9 (m, 16H, ArH & 2CH) [Found : C, 71.52, H, 4.15, N, 10.86, C ₂₃ H ₁₆ ClN ₃ O requires C, 71.59, H, 4.18, N, 10.89%]
4o	C ₆ H ₅	OCH ₃	H	OH	H	268-270	IR: 3129 (OH), 3027 (CH-Str), 1652 (C=N)
4p	C ₆ H ₅	OCH ₃	H	OCH ₃	OH	257-260	IR: 3126 (OH), 3031 (CH-Str), 1654 (C=N)
4q	C ₆ H ₅	OH	H	H	H	255-257	IR: 3130 (OH), 3026 (CH-Str), 1648 (C=N)
4r	C ₆ H ₅	OH	H	OCH ₃	H	270-272	IR: 3128 (OH), 3030 (CH-Str), 1642 (C=N)
4s	C ₆ H ₅	OH	H	Cl	H	247-250	IR: 3138 (OH), 3027 (CH-Str), 1649 (C=N)
4t	C ₆ H ₅	OCH ₃	OH	OH	H	245-248	IR: 3132 (OH), 3026 (CH-Str), 1664 (C=N), ¹ H NMR: 3.5 (s, 3H, OCH ₃), 5.5 (br,1H,OH), 6.7- 8.0(m, 14H, ArH & 2CH), 9.4(br,1H,OH), ¹³ C NMR: 55.11(OCH ₃), 112.92(CH), 119.33(C=C), 125.19-133.47(Ar-C), 147.29(C=N), 147.97(C=N), 150.20(C=N). [Found : C, 69.66, H, 4.60, N, 10.12, C ₂₄ H ₁₉ N ₃ O ₄ requires C, 69.72, H, 4.63, N, 10.16%]
4u	C ₆ H ₅	OCH ₃	OH	OCH ₃	OH	238-240	IR: 3125 (OH), 3030 (CH-Str), 1664 (C=N), ¹ H NMR: 3.6 (s, 3H, OCH ₃), 3.8 (s, 3H, OCH ₃) 6.7- 8.0(m, 13H, ArH & 2CH), 9.9(br,1H,OH), 11.3(br,1H,OH), ¹³ C NMR: 55.16(OCH ₃), 55.58(OCH ₃), 112.96(CH), 120.08(C=C), 124.18-133.88(Ar-C), 147.29(C=N), 147.86(C=N), 150.19(C=N). [Found : C, 67.68, H, 4.62, N, 9.48, C ₂₅ H ₂₁ N ₃ O ₅ requires C, 67.71, H, 4.77, N, 9.48%]



Scheme-1

Table-2: Antibacterial activity of compound 4

Compounds	Zone of Inhibition (in mm)			
	Gram Positive		Gram Negative	
	<i>S.aureus</i>	<i>C.diphtheria</i>	<i>P.aeruginosa</i>	<i>E.coli</i>
4a	8	9	12	12
4d	9	11	14	10
4e	11	8	12	12
4i	9	10	10	11
4n	8	11	11	10
4o	10	11	12	14
4q	12	10	14	12
4t	13	16	18	14
4u	14	18	18	15
Ampicillin trihydrate	26	28	24	21
DMSO	00	00	00	00

* Diameter of the disc was 6 mm, concentration of the compounds taken was about 100 µg/mL.